



Relationship of hypertension to coronary atherosclerosis and cardiac events in patients with coronary computed tomographic angiography

Nakanishi, Rine ; Baskaran, Lohendran ; Gransar, Heidi ; Budoff, Matthew J ; Achenbach, Stephan ; Al-Mallah, Mouaz ; Cademartiri, Filippo ; Callister, Tracy Q ; Chang, Hyuk-Jae ; Chinnaiyan, Kavitha ; Chow, Benjamin J W ; DeLago, Augustin ; Hadamitzky, Martin ; Hausleiter, Joerg ; Cury, Ricardo ; Feuchtner, Gudrun ; Kim, Yong-Jin ; Leipsic, Jonathon ; Kaufmann, Philipp A ; Maffei, Erica ; Raff, Gilbert ; Shaw, Leslee J ; Villines, Todd C ; Dunning, Allison ; Marques, Hugo ; Pontone, Gianluca ; Andreini, Daniele ; Rubinshtein, Ronen ; Bax, Jeroen ; Jones, Erica ; Hindoyan, Niree ; Gomez, Millie ; Lin, Fay Y ; Min, James K ; Berman, Daniel S

Abstract: Hypertension is an atherosclerosis factor and is associated with cardiovascular risk. We investigated the relationship between hypertension and the presence, extent, and severity of coronary atherosclerosis in coronary computed tomographic angiography and cardiac events risk. Of 17 181 patients enrolled in the CONFIRM registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) who underwent 64-detector row coronary computed tomographic angiography, we identified 14 803 patients without known coronary artery disease. Of these, 1434 hypertensive patients were matched to 1434 patients without hypertension. Major adverse cardiac events risk of hypertension and non-hypertensive patients was evaluated with Cox proportional hazards models. The prognostic associations between hypertension and no-hypertension with increasing degree of coronary stenosis severity (nonobstructive or obstructive 50%) and extent of coronary artery disease (segment involvement score of 1-5, >5) was also assessed. Hypertension patients less commonly had no coronary atherosclerosis and more commonly had nonobstructive and 1-, 2-, and 3-vessel disease than the no-hypertension group. During a mean follow-up of 5.2 ± 1.2 years, 180 patients experienced cardiac events, with 104 (2.0%) occurring in the hypertension group and 76 (1.5%) occurring in the no-hypertension group (hazard ratios, 1.4; 95% confidence intervals, 1.0-1.9). Compared with no-hypertension patients without coronary atherosclerosis, hypertension patients with no coronary atherosclerosis and obstructive coronary disease tended to have higher risk of cardiac events. Similar trends were observed with respect to extent of coronary artery disease. Compared with no-hypertension patients, hypertensive patients have increased presence, extent, and severity of coronary atherosclerosis and tend to have an increase in major adverse cardiac events.

DOI: <https://doi.org/10.1161/HYPERTENSIONAHA.117.09402>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-137887>

Journal Article

Published Version

Originally published at:

Nakanishi, Rine; Baskaran, Lohendran; Gransar, Heidi; Budoff, Matthew J; Achenbach, Stephan; Al-Mallah, Mouaz; Cademartiri, Filippo; Callister, Tracy Q; Chang, Hyuk-Jae; Chinnaiyan, Kavitha; Chow, Benjamin J W; DeLago, Augustin; Hadamitzky, Martin; Hausleiter, Joerg; Cury, Ricardo; Feuchtner, Gudrun; Kim, Yong-Jin; Leipsic, Jonathon; Kaufmann, Philipp A; Maffei, Erica; Raff, Gilbert; Shaw, Leslee J; Villines, Todd C; Dunning, Allison; Marques, Hugo; Pontone, Gianluca; Andreini, Daniele; Rubinshtein, Ronen; Bax, Jeroen; Jones, Erica; Hindoyan, Niree; Gomez, Millie; Lin, Fay Y; Min, James K; Berman, Daniel S (2017). Relationship of hypertension to coronary atherosclerosis and cardiac events in patients with coronary computed tomographic angiography. *Hypertension*, 70(2):293-299.
DOI: <https://doi.org/10.1161/HYPERTENSIONAHA.117.09402>

Relationship of Hypertension to Coronary Atherosclerosis and Cardiac Events in Patients With Coronary Computed Tomographic Angiography

Rine Nakanishi, Lohendran Baskaran, Heidi Gransar, Matthew J. Budoff, Stephan Achenbach, Mouaz Al-Mallah, Filippo Cademartiri, Tracy Q. Callister, Hyuk-Jae Chang, Kavitha Chinnaiyan, Benjamin J.W. Chow, Augustin DeLago, Martin Hadamitzky, Joerg Hausleiter, Ricardo Cury, Gudrun Feuchtnner, Yong-Jin Kim, Jonathon Leipsic, Philipp A. Kaufmann, Erica Maffei, Gilbert Raff, Leslee J. Shaw, Todd C. Villines, Allison Dunning, Hugo Marques, Gianluca Pontone, Daniele Andreini, Ronen Rubinshtein, Jeroen Bax, Erica Jones, Niree Hindoyan, Millie Gomez, Fay Y. Lin, James K. Min, Daniel S. Berman

Abstract—Hypertension is an atherosclerosis factor and is associated with cardiovascular risk. We investigated the relationship between hypertension and the presence, extent, and severity of coronary atherosclerosis in coronary computed tomographic angiography and cardiac events risk. Of 17 181 patients enrolled in the CONFIRM registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) who underwent ≥ 64 -detector row coronary computed tomographic angiography, we identified 14 803 patients without known coronary artery disease. Of these, 1434 hypertensive patients were matched to 1434 patients without hypertension. Major adverse cardiac events risk of hypertension and non-hypertensive patients was evaluated with Cox proportional hazards models. The prognostic associations between hypertension and no-hypertension with increasing degree of coronary stenosis severity (nonobstructive or obstructive $\geq 50\%$) and extent of coronary artery disease (segment involvement score of 1–5, >5) was also assessed. Hypertension patients less commonly had no coronary atherosclerosis and more commonly had nonobstructive and 1-, 2-, and 3-vessel disease than the no-hypertension group. During a mean follow-up of 5.2 ± 1.2 years, 180 patients experienced cardiac events, with 104 (2.0%) occurring in the hypertension group and 76 (1.5%) occurring in the no-hypertension group (hazard ratios, 1.4; 95% confidence intervals, 1.0–1.9). Compared with no-hypertension patients without coronary atherosclerosis, hypertension patients with no coronary atherosclerosis and obstructive coronary disease tended to have higher risk of cardiac events. Similar trends were observed with respect to extent of coronary artery disease. Compared with no-hypertension patients, hypertensive patients have increased presence, extent, and severity of coronary atherosclerosis and tend to have an increase in major adverse cardiac events. (*Hypertension*. 2017;70:00-00. DOI: 10.1161/HYPERTENSIONAHA.117.09402.)

Key Words: angiography ■ atherosclerosis ■ coronary artery disease ■ hypertension ■ risk factors

Received March 16, 2017; first decision March 25, 2017; revision accepted May 14, 2017.

From the Los Angeles BioMedical Research Institute at Harbor UCLA Medical Center, Torrance, CA (R.N., M.J.B.); Departments of Imaging and Medicine, Cedars-Sinai Medical Center, Los Angeles, CA (R.N., H.G., D.S.B.); Department of Radiology, Dalio Institute of Cardiovascular Imaging, New York-Presbyterian Hospital and Weill Cornell Medicine (L.B., E.J., N.H., M.G., F.Y.L., J.K.M.); Department of Medicine, University of Erlangen, Germany (S.A.); King Saudbin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, King AbdulAziz Cardiac Center, Ministry of National Guard, Health Affairs, Riyadh, Saudi Arabia (M.A.-M.); Department of Radiology, Montreal Heart Institute, Quebec, Canada (F.C., E.M.); Department of Radiology, Erasmus University Medical Center, Rotterdam, The Netherlands (F.C., E.M.); Tennessee Heart and Vascular Institute, Hendersonville (T.Q.C.); Division of Cardiology, Severance Cardiovascular Hospital and Severance Biomedical Science Institute, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea (H.-J.C.); William Beaumont Hospital, Royal Oaks, MI (K.C., G.R.); Department of Medicine and Radiology, University of Ottawa, Ontario, Canada (B.J.W.C.); Capitol Cardiology Associates, Albany, New York (A.D.); Department of Radiology and Nuclear Medicine, German Heart Center Munich, Germany (M.H.); Medizinische Klinik und Poliklinik I, Ludwig-Maximilians-Universität München, Germany (J.H.); Baptist Cardiac and Vascular Institute, Miami, FL (R.C.); Department of Radiology, Medical University of Innsbruck, Austria (G.F.); Department of Medicine and Radiology, Seoul National University Hospital, South Korea (Y.-J.K.); Department of Medicine and Radiology, University of British Columbia, Vancouver, Canada (J.L.); Department of Nuclear Cardiology, Cardiovascular Center, University Hospital, Zurich, Switzerland (P.A.K.); Department of Cardiology, Emory University School of Medicine, Atlanta, GA (L.J.S.); Department of Medicine, Walter Reed National Military Medical Center, Bethesda, MD (T.C.V.); Duke Clinical Research Institute, Durham, NC (A.D.); UNICA, Cardiac CT and MRI Unit, Hospital da Luz, Lisbon, Portugal (H.M.); Department of Clinical Sciences and Community Health, University of Milan, Italy (G.P., D.A.); Centro Cardiologico Monzino, IRCCS, Italy (G.P., D.A.); Department of Cardiology at the Lady Davis Carmel Medical Center, The Ruth and Bruce Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel (R.R.); and Department of Cardiology, Leiden University Medical Center, HARTZ, The Netherlands (J.B.).

Correspondence to Daniel S. Berman, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Los Angeles, CA 90048. E-mail BermanD@csshs.org

© 2017 American Heart Association, Inc.

Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.117.09402

Hypertension affects almost one third of adults, including >7 million patients in the United States^{1–3} and is strongly associated with cardiovascular morbidity and mortality.^{4–9} Although hypertension is a well-established risk factor for coronary artery disease (CAD),¹⁰ the relationships between hypertension and coronary atherosclerotic plaque stenosis, extent, characteristics, and major adverse cardiac events (MACE) risk have not been examined. Coronary computed tomographic angiography (CTA) has emerged as an accurate noninvasive modality to evaluate coronary atherosclerotic plaque and assess the risk of patients with suspected CAD.^{11–14} In this study, we used coronary CTA to investigate the relationship between hypertension and the presence, extent, and severity of CAD and to explore whether hypertension adds to the assessment of atherosclerosis in prediction of MACE.

Methods

Study Population

From 17181 patients enrolled in the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) registry between 2002 and 2011 who underwent ≥64-detector row coronary CTA at 17 centers, we identified 14803 patients without known CAD who underwent coronary CTA. Of those, we sequentially excluded patients without information on MACE (n=6889), early revascularization <3 months after coronary CTA (n=1212), and any risk factors used for matching (n=2272), resulting in a population of 4430 patients. Hypertensive and nonhypertensive subjects were matched for age, sex, all other CAD risk factors, including diabetes mellitus, dyslipidemia, current smoking, family history, chest pain symptoms (asymptomatic, atypical, noncardiac, and typical chest pain), and dyspnea using propensity scores.¹⁵ The resulting propensity score was then applied 1:1 to match every hypertensive subject (n=2791) to a corresponding nonhypertensive subject (n=1639) using a Mahalanobis nearest-neighbor matching algorithm with caliper <0.01.¹⁵ After matching, 2868 patients (age 56.4±11.1 years, male 60.8%) comprised the final study population, with 1434 patients with hypertension and 1434 patients without hypertension. The study was followed by Declaration of Helsinki Guidelines, and each institution obtained Institutional Review Board approval. All patients had signed informed consent.

Prescan Risk Factor Assessment

All CAD risk factors were prospectively ascertained before the coronary CTA examination by direct patient interview by a physician or nurse research coordinator and by standardized site surveys. Hypertension was defined as a history of physician-diagnosed high blood pressure or treatment with blood pressure medications. Dyslipidemia was defined as physician-diagnosed dyslipidemia or current treatment with lipid-lowering medications. Diabetes mellitus was defined by physician-diagnosed diabetes mellitus or use of insulin or oral hypoglycemic agents. A smoking history was defined as current smoking or cessation of smoking within 3 months of testing. Family history of CAD was determined by self-report. Chest symptom characteristics (asymptomatic, atypical, noncardiac, and typical chest pain and dyspnea) were recorded.¹⁶

Imaging Analysis

Coronary CTA was performed using multidetector CT scanners with ≥64 slices detector rows as previously described.^{14,17} CT data sets were evaluated for the presence of any plaque and plaque composition (stenosis and extent) on coronary CTA, using a modified 16-segment American Heart Association coronary tree model in accordance with the Society of Cardiovascular Computed Tomographic guidelines.¹⁸ Coronary plaque was identified as hyperdense structure adjacent to lumen of any size or hypodense structure distinct from lumen and

per-arterial tissue >1 mm² in largest area. Severity of luminal stenosis was classified into 3 groups: none (0% luminal stenosis), nonobstructive (1%–49% luminal stenosis), and obstructive stenosis (≥50% luminal stenosis). For per-vessel analysis, we used a 5-group categorization: no plaque, nonobstructive CAD, and presence of obstructive CAD in 1, 2, or 3 vessels. Left main disease was categorized as a 3-vessel CAD equivalent. For measures of CAD extent and distribution, the segment involvement score (SIS) was defined as the total number of coronary artery segments involved with any plaque.¹³ For per-location analysis, we used a 5-group categorization: left main, proximal, mid and distal coronary segments, and side branches, including diagonal branches, obtuse marginal branches, posterior descending artery, and posterior lateral branch. Detected plaques were visually classified as noncalcified plaque (containing no calcification), partially calcified plaque (containing calcification and noncalcified plaque), or calcified plaque (containing only calcification).

Statistical Analysis

Continuous variables were expressed as the mean±SD. The Wilcoxon rank-sum test (for nonparametrically distributed variables) was used to conduct intergroup comparisons between no-hypertension and hypertension groups. Categorical variables were compared using Pearson χ^2 tests.

MACE was defined as all-cause death or nonfatal myocardial infarction. Myocardial infarction was defined by site physicians in accordance with American College of Cardiology/American Heart Association guidelines and the World Health Organization Universal Definition of Myocardial Infarction.^{19,20} The log-rank test was used for comparing MACE event rates between the hypertension and no-hypertension groups, and MACE-free survival was further assessed using Cox proportional hazards models and Kaplan–Meier survival curves. We also assessed MACE risk by Cox proportional hazards models in men and women.

In addition, degrees of stenosis severity (normal, nonobstructive, and obstructive CAD ≥50%) and extent of CAD (SIS of 0, 1–5, and >5) were assessed among no-hypertension and hypertension groups in relation to time to MACE by Cox proportional hazards models. Scaled Schoenfeld residuals were used to verify the assumption of proportional hazards of the Cox models.²¹ Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated from the Cox models. Area under the curves (AUC) by receiver operator characteristics for prediction of MACE were used to evaluate the added value of hypertension over assessment of coronary atherosclerosis alone (≥50% stenosis or SIS) or the combination of coronary atherosclerosis and clinical factors other than hypertension (other clinical factors [age, sex, diabetes mellitus, dyslipidemia, current smoking, family history, and all chest symptoms]). We also calculated continuous net reclassification index (cNRI)²² between the models to investigate whether hypertension reclassified patients with respect to MACE risk over the combination of other clinical risk factors and atherosclerosis variables.

All statistical calculations were performed using STATA (Version 11.2; StataCorp LP, College Station, TX) for Windows.

Results

Patient Characteristics

Table 1 demonstrates the baseline characteristics among patients with and without hypertension. Propensity matching resulted in no differences between the groups in age, male sex, other CAD risk factors, and all chest symptoms ($P>0.05$ for all).

CAD Characteristics on Coronary CTA

Extent and severity of CAD as observed on coronary CTA in patients with and without hypertension are shown in Table 2. About plaque extent and severity stenosis, compared with the no-hypertension patients, hypertension patients manifested a greater SIS and a lower prevalence of absent

Table 1. Clinical Characteristics (n=2868)

Clinical Characteristics	No Hypertension (n=1434)	Hypertension (n=1434)	PValue
Age	56.3±11.0	56.6±11.1	0.47
Male sex (%)	60.8	60.8	1.00
Diabetes mellitus (%)	7.5	8.5	0.30
Dyslipidemia (%)	48.0	49.0	0.60
Smoking (%)	16.5	18.3	0.20
Family history (%)	33.3	34.8	0.41
Chest pain status (%)			
Asymptomatic	39.8	37.7	0.17
Noncardiac	14.2	15.8	
Atypical	37.3	35.9	
Typical	8.8	10.7	
Dyspnea	12.8	14.6	0.44

plaque. Hypertension patients possessed greater prevalence of obstructive lesions in 1, 2, or 3 vessels ($P<0.001$). Hypertension patients had more $\geq 50\%$ stenosis in the proximal and mid coronary arteries and side branches. On plaque characteristics, any noncalcified plaque or calcified plaque was more observed in hypertension patients compared with no-hypertension patients (Table 2).

MACE Risk

One-hundred eighty patients (6.3% of study population) experienced MACE at a mean follow-up of 5.2 ± 1.2 years, occurring in 104 patients of the hypertension group and 76 patients of the no-hypertension group (42 deaths, 34 nonfatal myocardial infarction; 7.3% versus 5.3%, $P=0.03$; Tables 3 and 4). Kaplan–Meier curve demonstrated that MACE were more common in the hypertension versus the no-hypertension subjects ($P<0.01$; Figure 1). By Cox proportional analysis, hypertension subjects experienced higher MACE risk than no-hypertension subjects (HR, 1.4; 95% CI, 1.0–1.9; $P=0.03$). On a subanalysis by sex, in both of men and women, MACE tended to be more common in the hypertension versus the no-hypertension subjects (HR, 1.4; 95% CI, 0.9–2.0; $P=0.12$ for men, and HR, 1.4; 95% CI, 0.9–2.3; $P=0.14$ for women).

Considering the CTA findings, the risk of MACE was progressively higher in the subjects with nonobstructive CAD and those with obstructive CAD when compared with those with no-CAD (Figure 2A). A trend toward a higher odds ratio was observed among hypertension patients with normal coronary arteries; however, it did not reach statistical significance (HR, 1.9; 95% CI, 1.0–3.6; $P=0.06$). In patients with nonobstructive CAD, the HRs of the hypertension and no-hypertension groups were similar. In the obstructive CAD group, the HR in the hypertension group was only slightly higher than that in the no-hypertension group (Figure 2A).

On the extent of CAD, similar findings were observed. The risk of MACE was also progressively higher in the subjects with SIS of 1 to 5 and those with SIS of >5 when compared with those with no-CAD. The HRs of the hypertension

Table 2. CAD Characteristics on Coronary CTA (n=2868)

CAD Characteristics on Coronary CTA	No Hypertension (n=1434)	Hypertension (n=1434)	PValue
SIS (median; IQR)	0 (0–2)	1 (0–3)	<0.0001
No. of vessels with plaque and $\geq 50\%$ stenosis (%)			
No plaque	53.0	43.7	<0.001
Nonobstructive plaque (1%–49%)	33.3	37.7	
1-vessel disease ($\geq 50\%$)	9.5	12.1	
2-vessel disease ($\geq 50\%$)	2.6	4.4	
3-vessel disease ($\geq 50\%$)/Left main	1.6	2.2	
Distribution for any coronary artery disease (%)			
Left main	12.6	14.1	0.24
Proximal	38.2	46.6	<0.001
Mid	29.3	36.0	<0.001
Distal	14.1	18.6	0.002
Side branches	14.7	18.4	0.01
Distribution for coronary artery disease with $\geq 50\%$ stenosis (%)			
Left main	0.3	0.6	0.18
Proximal	7.5	10.0	0.02
Mid	8.2	10.3	0.06
Distal	3.4	4.6	0.12
Side branches	4.7	7.0	0.01
Plaque characteristics (%)			
Noncalcified plaque	13.2	17.8	0.001
Partially calcified plaque	19.5	22.2	0.08
Calcified plaque	24.3	28.2	0.02

CAD indicates coronary artery disease; CTA, computed tomographic angiography; IQR, interquartile range; and SIS, segment involvement score.

group in the SIS of 1 to 5 and SIS of >5 groups were only slightly higher than the no-hypertension group (Figure 2B).

The incremental added value of hypertension in prediction of MACE over clinical and CTA variables is shown in Table 4. The presence of obstructive CAD was predictive of MACE (model 1; AUC, 0.648). The combination of other clinical factors increased this prediction (model 2; $P<0.0001$ for cNRI and $P<0.0001$ for AUC). When hypertension was then added (model 3), there was a significant increase in cNRI ($P=0.03$), and a trend toward increase in the AUC ($P=0.055$). Similar

Table 3. MACE Risk

MACE Risk			
MACE	No Hypertension (n=1434)	Hypertension (n=1434)	PValue
MACE (% , n)	5.3 (76)	7.3 (104)	0.03
Deaths (% , n)	2.9 (42)	3.9 (56)	
Nonfatal MI (% , n)	2.4 (34)	3.4 (48)	

MACE indicates major adverse cardiac events; and MI, myocardial infarction.

Table 4. Predictors of MACE

Predictors of MACE						
Models	cNRI (95% CI)	P Value	% Events Reclassified	% Nonevents Reclassified	AUC	AUC P Value
Stenosis severity of CAD						
Model 1	0.648	
Model 2 (vs model 1)	0.39 (0.24–0.54)	<0.0001	14%, $P=0.053$	24%, $P<0.0001$	0.729	<0.0001
Model 3 (vs model 2)	0.17 (0.02–0.32)	0.03	16%, $P=0.04$	1%, $P=0.59$	0.734	0.055
Extent of CAD						
Model 4	0.678	
Model 5 (vs model 4)	0.41 (0.26–0.56)	<0.0001	17%, $P=0.03$	24%, $P<0.0001$	0.721	0.001
Model 6 (vs model 5)	0.17 (0.02–0.32)	0.03	16%, $P=0.04$	1%, $P=0.59$	0.726	0.052

Model 1: Stenosis severity $\geq 50\%$. Model 2: Age, sex, and other risk factors+stenosis severity $\geq 50\%$. Model 3: Age, sex, and other risk factors+stenosis severity $\geq 50\%$ +HT. Model 4: SIS. Model 5: Age, sex, and other risk factors+SIS. Model 6: Age, sex, and other risk factors+SIS+HT. Other risk factors are diabetes mellitus, dyslipidemia, smoking, family history, and chest symptoms. AUC indicates area under the curve; CAD, coronary artery disease; CI, confidence interval; cNRI, continuous net reclassification index; HT, hypertension; MACE, major adverse cardiac events; MI, myocardial infarction; and SIS, segment involvement score.

results were observed with respect to the extent of CAD. The SIS alone was predictive MACE (model 4; AUC, 0.678). The combination of other clinical factors increased this prediction (model 5; $P<0.0001$ for cNRI and $P=0.0001$ for AUC). When hypertension was added (model 6), a significant increase in cNRI ($P=0.03$) and an increase in the AUC were observed ($P=0.052$).

Discussion

This study demonstrated that patients with hypertension had more advanced coronary atherosclerosis by coronary CTA and future MACE risk compared with those without hypertension. When stratifying by sex, there was a trend toward increased MACE risk in hypertension in both men and women. Patients with hypertension more frequently had any CAD, with higher prevalence of any CAD and of 1-, 2-, and 3-vessel obstructive CAD in each category, as well as CAD $\geq 50\%$ stenosis in the proximal, mid, and side branches. Hypertension patients also had greater prevalence of any noncalcified plaque and calcified plaque. When stratifying by the extent and severity of CAD, MACE risk in the hypertension group was slightly higher than that in the non-hypertension group across the

CAD categories. There was a trend toward incremental predictive value of hypertension over other risk factors and the extent or severity of CAD.

It is well known that hypertension is a main cardiovascular risk factor and related to worsening prognosis.^{4,5,7–9} To our knowledge, however, no previous studies have shown the direct relation of hypertension to CAD characteristics, including the presence, extent, and severity of CAD on coronary CTA and MACE risk that is described in this article.

Using the current registry, our group previously reported the relationship between diabetes mellitus and current smoking and the presence, extent, and severity of coronary atherosclerosis on coronary CTA, as well as the relationship of the coronary CTA findings to future adverse outcomes.^{23,24} The findings of this study suggest that the presence of hypertension per se may not add as much incremental prognostic value as these other risk factors after taking into account the presence, extent, and severity of coronary CTA.

Hypertension has been previously shown to be a predictor of the extent of coronary atherosclerosis as assessed by coronary artery calcium.²⁵ Both diabetes mellitus and smoking were found to be stronger predictors of coronary atherosclerosis than hypertension. Extensive epidemiological data have also demonstrated that hypertension is an independent risk factor for coronary atherosclerosis and for future cardiac events,^{26,27} but that it is less strong a predictor than diabetes mellitus and smoking.²⁵ Our findings are concordant with the previous data with respect to coronary atherosclerosis, including a relationship to increasing amounts of obstructive CAD and with showing a trend toward association with MACE events.

How hypertension results in increase in coronary atherosclerosis has been extensively studied. The principal underlying pathophysiologic mechanism is considered to be a mechanical one related to pulse pressure.²⁸ Wide pulse pressure has been reported to be associated with increased cardiac events.^{29–33} Both increased pulse pressure and systolic pressure contribute to endothelial dysfunction, which facilitates the entry of low-density lipid cholesterol into the blood vessel

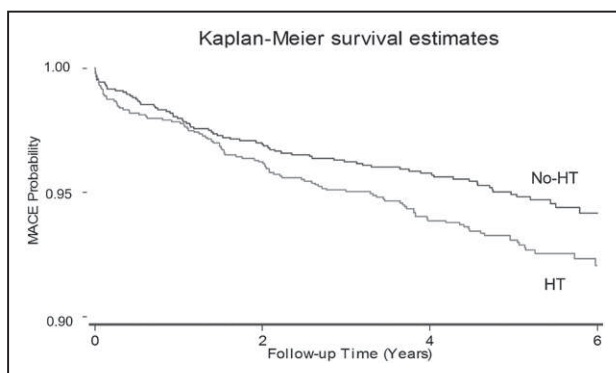


Figure 1. Kaplan–Meier curve for major adverse cardiac events (MACE) in patients with no known coronary artery disease (CAD) among the absence and presence of hypertension (HT).

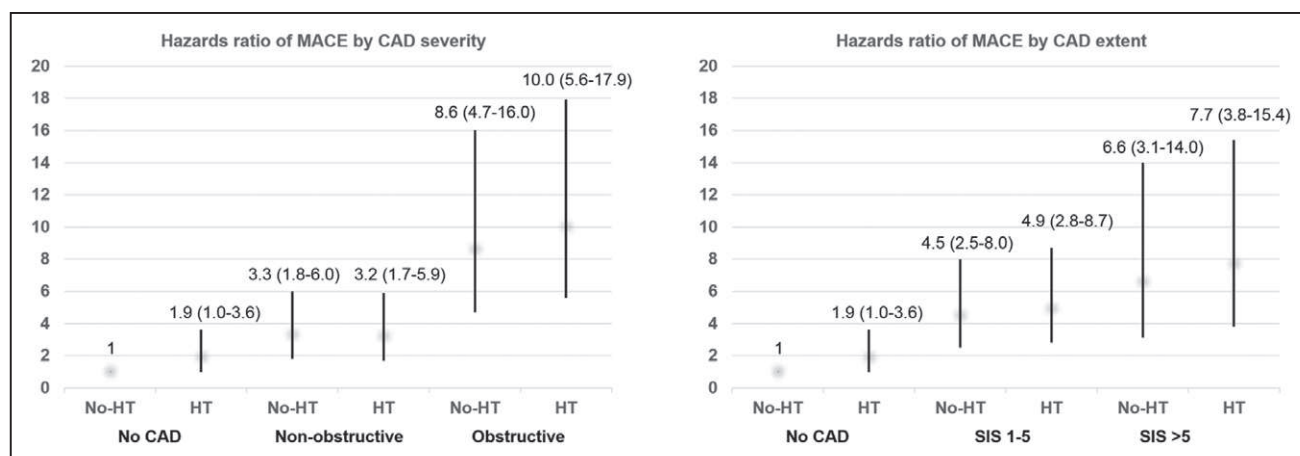


Figure 2. A, Left, Cox proportional hazard models by normal, nonobstructive, and obstructive coronary artery disease (CAD) among no-hypertension (no-HT) and hypertension (HT) groups. **B, Right,** Cox proportional hazard models by segment involvement score (SIS) 0, 1 to 5, and >5 among no-HT and HT groups.

wall, initiating the atherosclerotic process.³⁴ Hypertension also is a cause of left ventricular hypertrophy (LVH),^{35,36} which has been implicated as a cause of coronary atherosclerosis, myocardial infarction, arrhythmia, cardiac failure, or cardiac death.^{34,37–39} LVH is associated with collagen deposition within the left ventricle.³⁴ This process is considered to explain the frequent association of LVH with midmyocardial scarring on cardiovascular magnetic resonance, which is associated with increase in cardiac events.⁴⁰

Of interest, in this study, in patients with no evidence of CAD on coronary CTA, those with hypertension had a >2-fold MACE risk compared to those with no-hypertension. An increased risk of events in these patients could have been related to LVH; however, information on LVH was not present in the CONFIRM database.

Limitations

There are several limitations in this study. Data on duration and severity of hypertension, as well as information on LVH, did not exist in the current registry. Information was not uniformly available on specific antihypertensive medications at the time of testing. Further, no information was available on the effectiveness of blood pressure control after testing which may have affected MACE risk.⁴¹ We have included various CAD descriptors, including the extent, stenosis severity, basic characteristics, and location of CAD. However, other variables, such as vulnerable plaque features or bifurcation lesions, that might be associated with MACE risk were not available in this study. The number of events by sex was small and may have led to the finding that a trend toward increased MACE divided by sex was not statistically significant.

Perspectives

Compared with patients without hypertension, hypertensive patients have increased presence, extent, and severity of coronary atherosclerosis and tend to have an increase in MACE events. The findings support the concept of lifestyle modification regardless of sex to optimize CAD risk factors, including hypertension, to reduce future cardiovascular events as suggested by current guidelines.⁴²

Conclusions

Hypertensive patients had greater amount of coronary atherosclerosis and greater risk of MACE compared with nonhypertensive patients, independent of other clinical risk factors and of the presence of obstructive CAD or extent of CAD. Further, hypertensive individuals with an increasing degree of CAD stenosis severity and extent of CAD experienced modestly increase rates of MACE compared with nonhypertensive patients.

Disclosures

J.K. Min received modest speakers' bureau medical advisory board compensation and significant research support from GE Healthcare. D.S. Berman received grant funding from Siemens and GE Healthcare. S. Achenbach received grant support from Siemens and Bayer Schering Pharma and has served as a consultant for Servier. M. Al-Mallah received support from the American Heart Association, BCBS Foundation of Michigan, and Astellas. F. Cademartiri has served on the Speakers' Bureau of Guerbet and is a consultant for Guerbet, Servier, and Somahlution. K. Chinnaiyan received grant support from Bayer Pharma and Blue Cross Blue Shield Blue Care MI. B.J.W. Chow received research and fellowship support from GE Healthcare, research support from Pfizer and AstraZeneca, and educational support from TeraRecon. G. Pontone received grant support from GE Healthcare and Heartflow, and has served on the Speakers' Bureau of GE Healthcare, Bracco, and Medtronic. J. Hausleiter received a research grant from Siemens Medical Systems. P.A. Kaufmann received institutional research support from GE Healthcare and grant support from Swiss National Science Foundation. G. Raff received grant support from Siemens, Blue Cross Blue Shield Blue Care MI, and Bayer Pharma. All other authors report no conflicts.

References

- Ostchega Y, Yoon SS, Hughes J, Louis T. Hypertension awareness, treatment, and control—continued disparities in adults: United States, 2005–2006. *NCHS Data Brief*. 2008;3:1–8.
- Centers for Disease Control and Prevention (CDC). Vital signs: prevalence, treatment, and control of hypertension—United States, 1999–2002 and 2005–2008. *MMWR Morb Mortal Wkly Rep*. 2011;60:103–108.
- Roger VL, Go AS, Lloyd-Jones DM, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. 2012;125:e2–e220. doi: 10.1161/CIR.0b013e31823ac046.

4. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ; Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. *Lancet*. 2002;360:1347–1360. doi: 10.1016/S0140-6736(02)11403-6.
5. Staessen JA, Gasowski J, Wang JG, Thijs L, Den Hond E, Boissel JP, Coepe J, Ekblom T, Gueyffier F, Liu L, Kerlikowske K, Pocock S, Fagard RH. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet*. 2000;355:865–872.
6. Ezzati M, Vander Hoorn S, Lawes CM, Leach R, James WP, Lopez AD, Rodgers A, Murray CJ. Rethinking the “diseases of affluence” paradigm: global patterns of nutritional risks in relation to economic development. *PLoS Med*. 2005;2:e133. doi: 10.1371/journal.pmed.0020133.
7. Messerli FH. Hypertension and sudden cardiac death. *Am J Hypertens*. 1999;12:181S–188S.
8. Koyanagi S, Eastham C, Marcus ML. Effects of chronic hypertension and left ventricular hypertrophy on the incidence of sudden cardiac death after coronary artery occlusion in conscious dogs. *Circulation*. 1982;65:1192–1197.
9. Zipes DP, Wellens HJ. Sudden cardiac death. *Circulation*. 1998;98:2334–2351.
10. Kaplan NM, Opie LH. Controversies in hypertension. *Lancet*. 2006;367:168–176. doi: 10.1016/S0140-6736(06)67965-8.
11. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, Scherer M, Bellinger R, Martin A, Benton R, Delago A, Min JK. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol*. 2008;52:1724–1732. doi: 10.1016/j.jacc.2008.07.031.
12. Meijboom WB, Meijjs MF, Schuijff JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. *J Am Coll Cardiol*. 2008;52:2135–2144. doi: 10.1016/j.jacc.2008.08.058.
13. Min JK, Shaw LJ, Devereux RB, Okin PM, Weinsaft JW, Russo DJ, Lippolis NJ, Berman DS, Callister TQ. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol*. 2007;50:1161–1170. doi: 10.1016/j.jacc.2007.03.067.
14. Min JK, Dunning A, Lin FY, et al; CONFIRM Investigators. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol*. 2011;58:849–860. doi: 10.1016/j.jacc.2011.02.074.
15. Imbens G. The role of propensity score in estimating dose-response functions. 2000;87:706–710.
16. Abidov A, Rozanski A, Hachamovitch R, Hayes SW, Aboul-Enein F, Cohen I, Friedman JD, Germano G, Berman DS. Prognostic significance of dyspnea in patients referred for cardiac stress testing. *N Engl J Med*. 2005;353:1889–1898. doi: 10.1056/NEJMoa042741.
17. Min JK, Dunning A, Lin FY, et al. Rationale and design of the CONFIRM (Coronary CT Angiography EvaluationN For Clinical Outcomes: An International Multicenter) Registry. *J Cardiovasc Comput Tomogr*. 2011;5:84–92. doi: 10.1016/j.jcct.2011.01.007.
18. Abbara S, Arbab-Zadeh A, Callister TQ, Desai MY, Mamuya W, Thomson L, Weigold WG. SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr*. 2009;3:190–204. doi: 10.1016/j.jcct.2009.03.004.
19. Anderson JL, Adams CD, Antman EM, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction); American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; American Association of Cardiovascular and Pulmonary Rehabilitation; Society for Academic Emergency Medicine. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol*. 2007;50:e1–e157. doi: 10.1016/j.jacc.2007.02.013.
20. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *J Am Coll Cardiol*. 2007;50:2173–2195. doi: 10.1016/j.jacc.2007.09.011.
21. Grambsch P. Proportional hazards tests and diagnostics based on weighted residuals. 1994;81:515–526.
22. Pencina MJ, D’Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med*. 2011;30:11–21. doi: 10.1002/sim.4085.
23. Rana JS, Dunning A, Achenbach S, et al. Differences in prevalence, extent, severity, and prognosis of coronary artery disease among patients with and without diabetes undergoing coronary computed tomography angiography: results from 10,110 individuals from the CONFIRM (COronary CT Angiography EvaluationN For Clinical Outcomes): an International Multicenter Registry. *Diabetes Care*. 2012;35:1787–1794. doi: 10.2337/dc11-2403.
24. Nakanishi R, Berman DS, Budoff MJ, et al. Current but not past smoking increases the risk of cardiac events: insights from coronary computed tomographic angiography. *Eur Heart J*. 2015;36:1031–1040. doi: 10.1093/eurheartj/ehv013.
25. Kronmal RA, McClelland RL, Detrano R, Shea S, Lima JA, Cushman M, Bild DE, Burke GL. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2007;115:2722–2730. doi: 10.1161/CIRCULATIONAHA.106.674143.
26. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 pt B):2935–2959. doi: 10.1016/j.jacc.2013.11.005.
27. Conroy RM, Pyörälä K, Fitzgerald AP, et al; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24:987–1003. doi: 10.1016/S0195-668X(03)00114-3.
28. Lee TM, Lin YJ, Su SF, Chien KL, Chen MF, Liau CS, Lee YT. Relation of systemic arterial pulse pressure to coronary atherosclerosis in patients with mitral stenosis. *Am J Cardiol*. 1997;80:1035–1039.
29. Verdecchia P, Schillaci G, Reboldi G, Franklin SS, Porcellati C. Different prognostic impact of 24-hour mean blood pressure and pulse pressure on stroke and coronary artery disease in essential hypertension. *Circulation*. 2001;103:2579–2584.
30. Benetos A, Safar M, Rudnicki A, Smulyan H, Richard JL, Ducimetière P, Guize L. Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. *Hypertension*. 1997;30:1410–1415.
31. Madhavan S, Ooi WL, Cohen H, Alderman MH. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. *Hypertension*. 1994;23:395–401.
32. Mitchell GF, Moyé LA, Braunwald E, Rouleau JL, Bernstein V, Geltman EM, Flaker GC, Pfeffer MA. Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. SAVE investigators. Survival and Ventricular Enlargement. *Circulation*. 1997;96:4254–4260.
33. Blacher J, Staessen JA, Gierard X, Gasowski J, Thijs L, Liu L, Wang JG, Fagard RH, Safar ME. Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. *Arch Intern Med*. 2000;160:1085–1089.
34. Frohlich ED. State of the Art lecture. Risk mechanisms in hypertensive heart disease. *Hypertension*. 1999;34:782–789.
35. Khattar RS, Acharya DU, Kinsey C, Senior R, Lahiri A. Longitudinal association of ambulatory pulse pressure with left ventricular mass and vascular hypertrophy in essential hypertension. *J Hypertens*. 1997;15:737–743.
36. Pannier B, Brunel P, el Aroussy W, Lacolley P, Safar ME. Pulse pressure and echocardiographic findings in essential hypertension. *J Hypertens*. 1989;7:127–132.
37. Haider AW, Larson MG, Benjamin EJ, Levy D. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. *J Am Coll Cardiol*. 1998;32:1454–1459.

38. Vasan RS, Levy D. The role of hypertension in the pathogenesis of heart failure. A clinical mechanistic overview. *Arch Intern Med*. 1996;156:1789–1796.
39. Dunn FG, McLenachan J, Isles CG, Brown I, Dargie HJ, Lever AF, Lorimer AR, Murray GD, Pringle SD, Robertson JW. Left ventricular hypertrophy and mortality in hypertension: an analysis of data from the Glasgow Blood Pressure Clinic. *J Hypertens*. 1990;8:775–782.
40. O'Hanlon R, Grasso A, Roughton M, et al. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2010;56:867–874. doi: 10.1016/j.jacc.2010.05.010.
41. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116.
42. Eckel RH, Jakicic JM, Ard JD, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 pt B):2960–2984. doi: 10.1016/j.jacc.2013.11.003.

Novelty and Significance

What Is New?

- This study is the first study showing the relation of hypertension to the presence, extent, and severity of coronary artery disease on coronary computed tomographic angiography and to risk of major adverse cardiac events among patients without known coronary artery disease.

What Is Relevant?

- The presence of hypertension per se may not add as much incremental prognostic value as other risk factors after taking into account the pres-

ence, extent, and severity of coronary computed tomographic angiography.

Summary

Patients with hypertension had greater prevalence of extent and stenosis severity of coronary artery disease and modestly increased major adverse cardiac events risk compared with those without hypertension.



Hypertension

Relationship of Hypertension to Coronary Atherosclerosis and Cardiac Events in Patients With Coronary Computed Tomographic Angiography

Rine Nakanishi, Lohendran Baskaran, Heidi Gransar, Matthew J. Budoff, Stephan Achenbach, Mouaz Al-Mallah, Filippo Cademartiri, Tracy Q. Callister, Hyuk-Jae Chang, Kavitha Chinnaiyan, Benjamin J.W. Chow, Augustin DeLago, Martin Hadamitzky, Joerg Hausleiter, Ricardo Cury, Gudrun Feuchtner, Yong-Jin Kim, Jonathon Leipsic, Philipp A. Kaufmann, Erica Maffei, Gilbert Raff, Leslee J. Shaw, Todd C. Villines, Allison Dunning, Hugo Marques, Gianluca Pontone, Daniele Andreini, Ronen Rubinshtein, Jeroen Bax, Erica Jones, Niree Hindoyan, Millie Gomez, Fay Y. Lin, James K. Min and Daniel S. Berman

Hypertension. published online June 12, 2017;

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2017 American Heart Association, Inc. All rights reserved.

Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://hyper.ahajournals.org/content/early/2017/06/12/HYPERTENSIONAHA.117.09402>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Hypertension* is online at:
<http://hyper.ahajournals.org/subscriptions/>